In The United States Patent Office

In re Application of Pravin M. PATEL, *Stabilized Steroid Composition And Method for Its Preparation*

Serial No.: 10/762,652
Filing Date: 22 January 2004

DECLARATION UNDER 37 C.F.R. § 1.132

I, Keith Rotenberg, Ph.D., hereby make this Declaration under 37 Code of Federal Regulations § 1.132.

1) I respectfully believe that my academic training and professional experience qualify me as one of skill in the art of Food & Drug Administration regulatory affairs and pharmaceutical formulation science. I attach a copy of my *curriculum vitae* summarizing my academic training and professional experience.

2) One of skill in the art would understand that linoleic acid is an omega-6 acid. One of skill in the art would understand that safflower oil contains approximately 78% linoleic acid. I understand that the captioned patent application refers to linoleic acid as an "omega-3 acid," and refers to safflower oil as a source of "omega-3 acid." One of skill in the art would,

on reading the captioned patent application, understand that the reference to "omega-3" is a patent (*i.e.*, clearly visible; not hidden) typographical error, and that "omega-6" was intended.

3) I have read and understand the prior art of record, including Mark W. GRINSTAFF *et al., Methods for In Vivo Delivery...*, United States Letters Patent No. 5,560,156 combined with John E. HOOVER *et al., Remington's Pharmaceutical Sciences* pp. 956-71 (18th ed., 1990).

4) Hydrocortisone 17-butyrate is a topical steroidal anti-inflammatory agent. It is used topically. It is commercially available in The United States as a topical cream, a topical lotion, a topical ointment, and a topical solution. This is evidenced by the United States Food & Drug Administration's *Therapeutic Drug Equivalents* (Orange Book) listing for the drug product hydrocortisone 17-butyrate. (copy attached) These Food & Drug Administration records show that hydrocortisone 17-butyrate is only available as a topical drug product.

5) Hydrocortisone 17-butyrate is not currently available in the United States in any non-topical formulation. To the contrary, on information and belief formed after a reasonable inquiry, no non-topical drug product containing hydrocortisone 17-butyrate has been approved as safe and effective by The Federal Food & Drug Administration. The sale of such

a non-approved drug product would constitute the sale of an unapproved new drug product. This would violate The Federal Food, Drug & Cosmetics Act, 21 U.S.C.

6) Grinstaff *at e.g.*, 26:21-31; 26:45-51, enumerates many drugs potentially suitable for inclusion in the interior fill of his synthetic blood micro spheres. Grinstaff, however, fails to mention hydrocortisone 17-butyrate. This is not surprising because Grinstaff teaches an intravenous blood substitute, while hydrocortisone 17-butyrate is not recognized in the art as being acceptable for intravenous administration. Thus, an artisan of skill in the art to which Grinstaff pertains would not consider hydrocortisone 17-butyrate suitable for inclusion in Grinstaff's micro spheres.

7) Grinstaff at 26:6-31 teaches to fill his micro spheres with cytotoxic drugs, non-steroidal anti-inflammatory agents, steroids, or immunosuppressive agents.

8) Grinstaff teaches to dissolve these agents in a fluorocarbon, soybean oil, safflower oil, coconut oil, olive oil, cotton seed oil or other biocompatible oil.

9) Grinstaff, however, fails to teach that the fluorocarbon or bio-compatible oil must contain omega-6 acid. To the contrary, Grinstaff teaches to use

several oils (*e.g.*, fluorocarbons, coconut oil) which do not contain omega-6 acid.

10) Grinstaff also fails to mention that the fluorocarbon or bio-compatible oil must contain omega-6 acid in an amount sufficient to stabilize hydrocortisone 17-butyrate.

11) Hydrocortisone is not interchangeable with hydrocortisone 17-butyrate. For example, hydrocortisone 17-butyrate is approved only for topical administration. In contrast, hydrocortisone is approved for systemic administration as an intramuscular injection, as an enema and as an oral dosage. *See* Hoover at 965. The art of record cautions that while hydrocortisone may also be administered topically, "Systemic side effects can result from topical application." *Id.*

12) Similarly, hydrocortisone 17-butyrate degrades to hydrocortisone 21-butyrate. No evidence shows that hydrocortisone degrades into hydrocortisone 21-butyrate. Hydrocortisone lacks a butyrate moiety. Hydrocortisone would therefore not be expected to degrade into hydrocortisone 21-butyrate, nor into any other butyrate form.

13) The claimed invention shows how to stabilize an eczema cream. In contrast, Grinstaff teaches a synthetic blood substitute. One of skill in these two arts would not consider these two fields the same. Further, one

of skill in the art would not consider Grinstaff's blood substitute technology "reasonably pertinent" when formulating eczema creams.

14) Grinstaff teaches that his micro spheres are admirably stable. Grinstaff, at 34:53 to 35:22, notes that at body temperature, his micro spheres survive intact for at least a month. Grinstaff, at 38:5-36, teaches that to liberate drug contained in the micro spheres, one must dissolve the micro spheres with an organic solvent (Grinstaff uses mercaptoethanol). Grinstaff thus teaches that when a drug or medical imaging agent is included in his micro spheres, the spheres survive intact for at least a month before opening and releasing the drug.

15) This may be quite advantageous when administering a medical imaging agent. This would, however, render a topical medicine like hydrocortisone 17-butyrate inoperable. Adding hydrocortisone 17-butyrate to Grinstaff's micro spheres would sequester the hydrocortisone 17-butyrate, rendering it unavailable and ineffective.

16) Further, Grinstaff teaches that the micro spheres would sequester the hydrocortisone 17-butyrate for at least a month. Hydrocortisone 17-butyrate, however, is administered as a *skin cream*; thus, if the patient bathes at least once a month (a likely assumption for a patient who has access to prescription drugs such as hydrocortisone 17-butyrate) the

patient would wash away the intact micro spheres - and their drug load - before the drug is released.

17) A patient could conceivably open the micro spheres by washing the micro sphere-treated skin with an organic solvent such as mercaptoethanol. This would be counter-productive, however, because organic solvent dries and damages skin. Compounding the problem, hydrocortisone 17-butyrate is used to treat eczema - already sensitive skin - so washing eczema-affected skin with an organic solvent would *exacerbate* the eczema, not ameliorate it.

18) Grinstaff (alone or combined with Hoover) does not enable one of skill in the art to practice the claimed invention. This is for several reasons. First, Grinstaff teaches to encapsulate the fill material in a micro sphere. Encapsulating hydrocortisone 17-butyrate, however, would render it inactive.

19) Second, Grinstaff provides a laundry list of bio-compatible oils. Grinstaff, however, does nothing to guide the artisan towards the operable species and away from inoperable species. To the contrary, Grinstaff teaches that all these oils are interchangeable. Reading Grinstaff, an artisan would be as likely (or indeed, be more likely) to make an

inoperable (non-stabilized) formulation as an operable (stabilized) formulation.

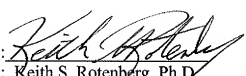
20) The prior art teaches that hydrocortisone 17-butyrate degrades into hydrocortisone 21-butyrate. Nothing in the prior art of record contradicts this. Thus, one of skill in the art would have expected that hydrocortisone 17-butyrate, whether or not incorporated into Grinstaff's micro spheres, would degrade into the 21-butyrate form.

21) In contrast to what the prior art teaches, the inventor has found a way to stabilize hydrocortisone 17-butyrate. The instant Specification shows that after 6 months of storage at 40° C, an eczema skin cream made without added omega-6 acid has **9.17%** total impurities (6.36 % hydrocortisone 21-butyrate and 2.81% other impurities). In contrast, the same skin cream with added omega-6 acid has only **5.56%** total impurities (5.00 % hydrocortisone 21-butyrate and 0.56% other impurities).

22) These results are of both statistical and practical significance. These results are statistically significant because the superior results shown in the instant patent application are not likely to be caused by random variation in the data. These results are practically significant because, as the Specification explains at 2:12-14, isomerization is of

particular concern to pharmaceutical formulators since the isomerization reaction raises therapeutic and regulatory issues regarding the efficacy and composition of isomerized compositions.

23) I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.

Signature : 
Name : Keith S. Rotenberg, Ph.D.
Dated as of : December 20, 2007

Attachments

Curriculum vitae.

The United States Food & Drug Administration's *Therapeutic Drug Equivalents* (Orange Book) listing for the drug product hydrocortisone 17-butyrate.

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PROFESSIONAL EXPERIENCE:

Triax Pharmaceuticals, LLC	July 2005 to present	Senior Vice President, Regulatory Affairs and Operations
Rotenberg Consultants, LLC	April 2005 to June 2005	President, Rotenberg Consultants, LLC, Denville, New Jersey
Reliant Pharmaceuticals	Sept. 2003 to March 2005	Senior Vice President, Research and Development, Reliant Pharmaceuticals, Liberty Corner, New Jersey
	2000 - 2003	Vice President, Regulatory Affairs, Reliant Pharmaceuticals, Liberty Corner, New Jersey
Rotenberg Consultants, LLC	2000 – 2000	Principal, Rotenberg Consultants, LLC, Denville, New Jersey
Forest Laboratories	1997-1999	Executive Director, Regulatory Affairs and Quality Operations, Forest Laboratories, Inc., Jersey City, New Jersey
Searle Pharmaceuticals	1996-1997	Senior Director, Corporate Licensing G.D.Searle, Skokie, Illinois
Lorex Pharmarmaceuticals	1989-1996	Senior Director, Department of Regulatory Affairs, Lorex Pharmaceuticals, Chicago, Illinois (a joint venture with Searle and Synthelabo)
Pennwalt Pharmaceuticals	1986-1988	Director, Division of Scientific Information and Regulatory Affairs, Pennwalt Corporation, Rochester, New York
	1984-1986	Associate Director, Clinical Pharmacology, Medical Department, Pennwalt Corporation, Rochester, New York
	1982-1984	Section Head, Biopharmaceutics, Medical Department, Pennwalt Corporation, Rochester, New York
Food and Drug Administration	1981-1982	Technical Supervisor, Food and Drug Administration, Bureau of Drugs, Division of Biopharmaceutics, Rockville, Maryland
	1977-1981	Pharmacologist, Food and Drug Administration, Bureau of Drugs, Division of Biopharmaceutics, Rockville, Maryland

DUTIES AND RESPONSIBILITIES:

Senior Vice President, Regulatory Affairs and Operations Triax Pharmaceuticals, LLC 7/05 to present:

Overall responsibilities for the Departments of Regulatory Affairs, Manufacturing, Research and Development, Clinical and Distribution.

Rotenberg Consultants, LLC 4/05 to 6/05

Rotenberg Consultants was formed to help pharmaceutical and related industry companies be successful when interacting with the FDA with respect to regulatory and quality assurance issues. The company provides services in the following areas: regulatory (IND, NDA, ANDA and DMF filings, strategy development, review of preclinical and clinical study reports, and training), FDA meeting preparation, promotion and advertising review, and quality assurance activities.

Senior Vice President, Research and Development Reliant Pharmaceuticals 9/03 to 3/05:

Overall responsibilities for the Departments of Clinical Development, Regulatory Affairs, Medical Affairs and Scientific Affairs. Directed the development program of six drug products in the following therapeutic areas: cardiovascular, gastro-intestinal, metabolic and anti-viral. These programs involved 25 Phase I studies (N= 924 subjects) and 8 Phase III studies (N = 1,730 patients). Three development programs received NDA approvals for products in the GI, Cardiovascular and Metabolic therapeutic areas. The approved development programs required formulation development, clinical studies and regulatory strategies that resulted in approvals within a 12 to 14 month period following filing. The remaining drug products are ongoing and involve new chemical entities requiring full drug development evaluation.

A member of Reliant's Operations Committee reporting to the CEO.

Developed the overall strategy for Research and Development programs leading to successful FDA approvals.

Global experience in developing clinical programs ex US that would meet US requirements for approval.

Directed the R&D effort concerning manufacturing site changes for solid and liquid dosage forms that resulted in FDA approvals.

Responsible for the R&D due diligence activities involving new chemical entities and patented drug products. This resulted in 9 drug products being licensed-in by Reliant Pharmaceuticals.

Co-author of several patents filed on products developed at Reliant.

Managed the R&D budget of approximately $30 million and a staff of 50 professionals.

Filed Reliant's first electronic NDA to FDA that resulted in an approval within 12 months following submission.

Created a Medical Science Liaison Department within Medical Affairs for Reliant.

Vice President, Regulatory Affairs Reliant Pharmaceuticals 9/00 to 9/03:

Overall responsibilities for Regulatory Affairs, Medical Affairs and Quality Assurance.

Created and staffed the Regulatory Affairs, Medical Affairs and Quality Assurance Departments.

Provided regulatory strategies for our development programs.

Participated in due diligence activities that resulted in acquiring several products for Reliant.

Principal, Rotenberg Consultants, LLC, 1/00 to 8/00:

Rotenberg Consultants was formed to help pharmaceutical and related industry companies be successful when interacting with the FDA with respect to regulatory and quality assurance issues. The company provides services in the following areas: regulatory (IND, NDA, ANDA and DMF filings, strategy development, review of preclinical and clinical study reports, and training), FDA meeting preparation, promotion and advertising review, and quality assurance activities.

Executive Director, Regulatory Affairs and Quality Operations, Forest Laboratories, Inc., 4/97 to 12/99:

Overall responsibility for the Regulatory Affairs, Quality Assurance, Quality

Control, Compliance (GMP and GCP) and Professional Affairs Departments. The Regulatory Affairs and Quality Operations Department staff was located in eight facilities (Commack, NY; Inwood, NY; Farmingdale, NY; Jersey City, NJ; St. Louis, MO (manufacturing facility and a distribution center); Dublin, Ireland; and London, England) and comprised a total staff of approximately 200 people.

Filed and negotiated the Celexa® (citalopram) NDA with FDA resulting in a successful launch of this $500 million dollar (plus) drug product.

Provided regulatory strategies for successful interactions with government regulatory authorities.

Global responsibility for regulatory and quality assurance.

Maintained effective communications with Government Agencies.

Hired experienced regulatory and QA/QC professionals to upgrade the Department.

Created a Professional Affairs Department to respond to healthcare professional and consumer/patient inquiries. This Department successfully handled 2000 telephone inquiries per month.

Developed an open communication atmosphere within the QA/QC Department such that facilities shared experiences (problems and solutions) during weekly teleconferences.

Served as Chairman of the Promotional and Advertising Committee.

Reorganized the Regulatory Affairs Department into a CMC group and FDA Liaison to effectively interact with FDA.

Successfully prepared the facilities (domestic and foreign) for five preapproval inspections.

Moved the Corporate Regulatory Affairs and Quality Operations Department from Manhattan to Jersey City with minimal amount of down time within the Department.

Senior Director, Corporate Licensing, G.D. Searle, 6/96 to 4/97:

Responsible for the licensing activities for the corporation associated with the Arthritis Franchise. These activities included signing of confidentiality agreements, negotiations of terms, initiation of scientific discussions with prospective licensees, reviewing

scientific literature for potential opportunities and evaluating the commercial opportunity for the company.

Senior Director, Department of Regulatory Affairs, Lorex Pharmaceuticals, 1/30/89 to 6/96:

Developed global strategies for effective interaction with government agencies with respect to investigational (United States, Canada, United Kingdom, Estonia, Poland, and Czechoslovakia) and new drug (United States and Canada) submissions (IND's, NDA's and NDS, etc.), drug promotion and advertising and deficiency letters. Responsible for regulatory compliance review and approval of advertising copy prior to use. Maintained effective communication between the company and government regulatory agencies. Within the company, provided guidance on clinical protocol development, evaluated study results and recommended additional clinical or preclinical studies to support the regulatory approval of the drug product.

Provided regulatory and clinical recommendations with respect to product licensing-in activities.

Hired and trained professionals (Ph.D., M.S. and B.S.) personnel for positions in regulatory affairs.

From September of 1993 to March 1994, Lorex was without a Clinical Research Director. During this period, in addition to my regulatory responsibilities, I assumed a lead role in the clinical development program for a new chemical entity. This included developing a full clinical plan, budget preparation, meeting outside experts in this specific clinical area and developing a multicenter 900 patient clinical protocol. Beyond this period, I continued to direct this program leading to an IND filing in July 1994.

Successfully filed, negotiated with FDA and launched Ambien® (zolpidem tartrate) a $450 million dollar per year product.

Director, Division of Scientific Information and Regulatory Affairs, Pennwalt Corporation, 1986 to 10/88:

Directed a staff of 25 professionals, prepared and managed a budget of over 1.5 million dollars. Maintained administrative responsibility for the Department of Regulatory Affairs, Research and Development Compliance Section, Biometrics Section and Information Services.

Developed and maintained a focal point within the Pharmaceutical Division for effective communication between the company and government regulatory agencies.

Created and maintained an effective Quality Assurance Unit for both Good Laboratory Practices for non-clinical studies and Good Clinical Practices.

Overall responsibility for the storage, electronic data processing, statistical analyses, retrieval, and utilization of information necessary for productive and efficient function of Research and Development.

Served as Chairman of the Label Copy Control Committee and maintained responsibility for keeping records of proposed and approved label copy. Responsible for regulatory compliance review and approval of advertising copy prior to use, and for distribution of proposed advertising copy for review and approval by other departments. Served as liaison in legal matters between the Pharmaceutical Division and Corporate Legal Department and outside Counsel.

Formulated strategies for interacting with government agencies with respect to investigational new drug submissions (IND's), new drug submissions (NDA's) drug advertising, and deficiency letters.

Associate Director, Clinical Pharmacology, Pennwalt Corporation, 1984 to 1986:

Directed and administered all Phase I clinical research. Developed study plans for Phase I safety studies in normal subjects and patients suitable for inclusion in submissions to regulatory agencies.

Prepared study plans for determination of pharmacokinetic/bioavailability parameters in human and experimental animal studies suitable for inclusion in submissions to regulatory agencies.

Developed methods for evaluating biopharmaceutical properties of formulations and dosage forms of investigational and marketed drugs.

Administered the daily operations of a professional staff, including budgeting considerations and sponsor negotiations.

Initiated contacts with clinical investigators and potential clinical investigators to determine their interest in and or availability to undertake a clinical study.

Directed the analysis of data, interpretation of results and prepared formal company reports on information generated from studies suitable for submission to regulatory agencies.

Evaluated in vitro/in vivo correlations and recommended dissolution specifications for

investigational new drugs. Designed and developed protocols to implement study plans and participate in monitoring performance of clinical and analytical investigators.

Met with regulatory agencies on issues of Phase I research, biopharmaceutics, pharmacokinetics and bioavailability.

Hired and trained professional (Ph.D. and B.S.) personnel with respect to Phase I research.

Section Head, Biopharmaceutics, Pennwalt Corporation, 1982 to 1984:

In conjunction with the medical staff within the Medical Department, developed study plans and protocols for evaluation of bioavailability/pharmacokinetics in humans and ensured that the experimental procedures, data analyses, and reporting of results embrace the current state-of-the-art and is satisfactory to governmental regulatory agencies.

Developed a biopharmaceutics section within the Medical Department to evaluate pharmacokinetic parameters and to design bioavailability protocols, clinical plans as well as monitor ongoing clinical studies to ensure regulatory compliance.

Technical Supervisor, Food and Drug Administration 1981 to 1982:

Responsible for the direction and evaluation of bioavailability/pharmacokinetic submissions contained in NDA's, Antibiotic Form 5, IND's and their amendments and supplements as performed by reviewer scientists composed of chemists, pharmacologists, biologists and pharmacists. This required a thorough knowledge of the regulations pertaining to the New Drug Approval process.

Chairman of the Division of Biopharmaceutics IND/NDA Rewrite Committee and Editor of the Guidelines for Conducting Pharmacokinetic, Bioavailability and Bioequivalence.

Member of the Bureau of Drugs' Task Force on Finished Dosage Products involved in revising the requirements for finished dosage products.

Responsible for making the Agency's determination whether a manufacturer has met all biopharmaceutic requirements which are necessary for NDA and Antibiotic Form 5 application approval or whether additional biopharmaceutical studies are necessary.

In conjunction with the performance of clinical drug studies, I have been involved in: 1) the developmental plans for the use of animal pharmacological techniques in support of biopharmaceutics research, 2) considering ways in which clinical and laboratory

findings concerning drug availability may be explored using animal models representing several species, and 3) evaluating and recommending the use of pharmacological endpoints as an alternative to chemical testing for drugs under study.

Pharmacologist, Food and Drug Administration 1977 to 1980:

Responsible for all NDA and IND submissions and supplements for the Division of Neuropharmacological Drug Products. In this capacity, I was responsible for all pharmacokinetic/biopharmaceutic reviews, and provided advice and recommendation to the Division as well as to drug firms on how to improve their biopharmaceutical submissions where existing protocols or studies were deficient.

Involved in a number of DESI announcements involving the assessment from petitions submitted by the regulated industry or from in-house information and the scientific literature regarding the applicability of an in vivo bioavailability and/or in vitro dissolution requirement to be imposed under 21 CFR 320. Handled approximately 30% of all NDE submissions submitted to the Division of Biopharmaceutics.

SOCIETY MEMBERSHIPS:

American Chemical Society
American Society for Clinical Pharmacology and Therapeutics
Drug Information Association
Regulatory Affairs Professional Society
American Association of Pharmaceutical Scientists

AWARDS AND HONORS:

Food and Drug Administration Award of Merit - May 22, 1981.
Who's Who in Frontiers of Science and Technology, 2nd Edition, 1985.

ACTIVITIES:

Chairman, Special Populations Workshop, sponsored by Pharmaceutical Manufacturers Association, Drug Metabolism Subsection, May 2, 1985, Washington, D.C.

Pharmaceutical Manufacturers Association Drug Metabolism Subsection Steering Committee, 1983-1987.

Chairman, Biopharmaceutics Considerations in NDA/ANDA Submissions, Drug Information Association, Nov. 10-13, 1985, Hilton Head, S.C.

Member of the Proprietary Association Phenylpropanolamine Working Party, 1988.

PAPERS PRESENTED:

1. Rotenberg, KS, Miller, RP, and Adir, J, Pharmacokinetics of Nicotine in Rats at Various Doses, Acad Pharm Sci, 5, 124 (1975).

2. Rotenberg, KS, Miller, RP, and Adir, J., Pharmacokinetics of Nicotine in Rats Following Cigarette Smoke Inhalation, Acad Pharm Sci, 6, 109 (1976).

3. Rotenberg, KS, Review of New FDA Guidelines, International Industrial Pharmacy Conference, Austin, Texas, February 24, 1981.

4. Amsel, LP, Hinsvark, ON, Rotenberg, KS, and Sheumaker, J, Recent Advances in Sustained Release Technology Utilizing Ion Exchange Polymers. Pharmaceutical Technology Conference, New York, September 1983.

5. Amsel, LP, Rotenberg, KS, Hinsvark, ON, and Sheumaker, J, Liquid Oral Controlled Release Products. Second Int'l Conference on Drug Absorption, Edinbaugh, Scotland, September 1983.

6. Raghunathan, Y, Amsel, LP, Hinsvark, ON, Rotenberg, KS, Diffusion Controlled Release of Drugs From Coated Drug Polymer Complex. American Chemical Society Meeting, Philadelphia, PA, August 26-31 1984.

7. Rotenberg, KS, Amsel, LP, Graves, DA, Hinsvark, ON, Woodworth, JR, The Development of a Sustained Release Pseudoephedrine Suspension Utilizing the Pennkinetic System. RXPO Meeting, New York, New York, June 18-21, 1984.

8. Woodworth, JR, Rotenberg, KS, Hinsvark, ON, Amsel, LP, Grozier, ML, Bioequivalence of Sustained Release Dextromethorphan (Delsym) and the Polymorphic Metabolism of Dextromethorphan. 13th Annual American College of Clinical Pharmacology, Philadelphia, PA, October 1984.

9. Graves, DA, Rotenberg, KS, Woodworth, JR, Amsel, LP, Hinsvark, ON, Bioavailability Assessment Methodologies Designed to Evaluate a New Controlled Release Pseudoephedrine Product. 19th Annual American Society of Hospital Pharmacists Midyear Meeting, Dallas, TX, December 1984.

10. Wecker, MT, Woodworth, JR, Hinsvark, ON, Amsel, LP, Rotenberg, KS, Comparative Pharmacokinetics of Two Doxepin Formulations. American College of Clin. Pharmacology, Poster Session II, October 1985.

11. Woodworth, JR, Locke, C, Hinsvark, ON, Raghunathan, Y, Amsel, LP, and Rotenberg, KS, A Pharmacokinetic/Pharmacodynamic Evaluation of a New Low Dose Metolazone Tablet Formulation, American Pharmaceutical Association 133rd Annual Meeting, March 16-20, 1986.

12. Rotenberg, KS, Human Testing Techniques: Bioavailability and Bioequivalence Testing Procedures to Evaluate Products, short course entitled "Practical Approaches to the Development of Controlled Release Products", sponsored by the American Pharmaceutical Association 133rd Annual Meeting, March 16-20, 1986.

13. Rotenberg, KS, Tailoring the European Dossier for Other Major Markets: USA, Eighth European Society of Regulatory Affairs Meeting, Barcelona, Spain, October 29-31, 1991.

14. McCallum, R, Zarling, E., Goetsch, CA, Griffin, C., Sarosiek, I, Rotenberg,KS, Nizatidine Controlled Release Has Gastric Prokinetic Effects in Patients with Gastroesophageal Reflux Disease, American College of Gastroenterology's 69th Annual Meeting, October 2004.

PUBLICATIONS:

1. Miller, RP, Adir, J, and Rotenberg, KS, Pharmacokinetics of Intravenous Nicotine in Rats, The Pharmacologist, 17, 193 (1975).

2. Adir, J, Miller, RP, Rotenberg, KS, Disposition of Nicotine in the Rat After Intravenous Administration, Res Com Chem Pathol Pharmacol, 13, 173 (1976).

3. Miller, RP. Rotenberg, KS, and Adir, J, Effect of Dose on the Pharmacokinetics of Intravenous Nicotine, Drug Met and Disp, 5, 436 (1977).

4. Rotenberg, KS, Miller, RP, and Adir, J, The Pharmacokinetics of Nicotine Following a Single Cigarette Smoke Inhalation in the Rat, J Pharm Sci, 69, 1087 (1980).

5. Straughn, AB, Meyer, MC, Raghow, G, and Rotenberg, KS, The Bioavailability of Microsize and Ultramicrosize Griseofulvin Products in Man, J Pharmacokinetics and Biopharmaceutics, 8, 347 (1980).

6. Rotenberg, KS, The Pharmacokinetics of Nicotine, Phar Int'l 3, 91 (1982).

7. Meyer, MC, Hwang, P, Straughn, AB, and Rotenberg, KS, HPLC Determination of Benzthiazide in Biologic Material, Biopharm Drug Disp, 3, 1 (1982).

8. Toothacker, RD, Sundaresan, GM, Hunt, SP, Goehl, TJ, Rotenberg, KS, Prasad, VK, Craig, WA, and Welling, PG, Oral Hydrocortisone Pharmacokinetics: A Comparison of Fluorescence and Ultraviolet High Pressure Liquid Chromatographic Assays for Hydrocortisone in Plasma, J Pharm Sci, 71, 573 (1982).

9. Rotenberg, KS, and Adir, J, Pharmacokinetics of Nicotine in Rats After Multiple Cigarette Smoke Exposure, Tox Applied Pharmacol, 69, 1 (1983).

10. Meyer, MC, Straugh, AB, Raghow, G, Schang, W, Rotenberg, KS, Absorption of Phenobarbital from Tablets and Elixir, J Pharm Sci, 73, 485, (1984).

11. Skelly, JP, and Rotenberg, KS, Pharmacokinetic Considerations in Drug Studies, Controlled Drug Bioavailability, Vol 2, pgs. 159-188. Edited by Dr. Victor F. Smolen and Dr. LuAnn Ball, Pub. John Wiley & Sons, Inc. (1984).

12. Amsel, LP, Hinsvark, ON, Rotenberg, KS, Sheumaker, J, Recent Advances in Sustained Release Technology Using Ion-Exchange Polymers, Pharmaceutical Technology, 8, 28 (1984).

13. PMA's Joint Committee on Bioavailability: The Role of Dissolution Testing in Drug Quality, Bioavailability, and Bioequivalence Testing, Pharmaceutical Technology, June (1985).

14. Graves, DA, Rotenberg, KS, Woodworth, JR, Amsel, LP, Hinsvark, ON, Bioavailability Assessment of a New Liquid Controlled Release Pseudoephedrine Product, Clin Pharm, 4, 199 (1985).

15. Wecker, MT, Woodworth, JR, Amsel, LP, Hinsvark, ON, and Rotenberg, KS, Pharmacokinetic Evaluation of Two Doxepin Products, Clin Ther, 8, 342 (1986).

16. Wecker, MT, Graves, DA, Amsel, LP, Hinsvark ON, Rotenberg, KS, Influence of a Standard Meal on the Absorption of Controlled-Release Pseudoephedrine Capsules, J Pharm Sci, 76, 29 (1987).

17. Woodworth, JR, Dennis, SRK, Moore, L, Rotenberg, KS, The Polymorphic Metabolism of Dextromethorphan, J Clin Pharmacol, 27, 133 (1987).

18. Woodworth, JR, Dennis, SRK, Hinsvark, ON, Amsel, LP, Rotenberg, KS, Bioavailability Evaluation of a Controlled-Release Dextromethorphan Liquid, J Clin Pharmacol, 27, 139 (1987).

19. Woodworth, JR, Ludden, TM, Ludden, LK, Shepherd, AMM, Rotenberg, KS, and Graves, DA, Controlled Release Hydralazine: Assessments of a Possible Interaction with Potassium Chloride, J Pharm Sci., 76, (1987).

20. Baumann, TJ, Bivins, BA, Graves, DA, Grozier, ML, Rotenberg, KS, Analgesic Safety and Efficacy of Controlled Release Hydrocodone, J Pharm Sci, 76, No. 11 (1987).

21. Adir, J, Janda, SM, Curry, CL, Taylor, RE, Poku, CD, Rotenberg, KS, Comparative Efficacy and Safety of Immediate-Release and Controlled-Release Hydralazine in Black Hypertensive Patients, Clin Ther, 9, 640 (1987).

22. Amsel, LP, Rotenberg, KS, Hinsvark, ON, Unique Oral Controlled Release Systems: In Vivo Drug Release Pattern. Oral Sustained Release Formulations: Design and Evaluation, Permagon Press, First Edition (1988).

23. Graves, DA, Woodworth, JR, Hinsvark, ON, and Rotenberg, KS, Single - and Multiple-Dose Bioavailability Studies of a Controlled-Release Pseudoephedrine Capsule Formulation, Curr Ther Res, 43, (1988).

24. Graves, DA, Wecker, MT, Meyer, MC, Straughn, AB, Amsel, LP, Hinsvark, ON, Bhargava, AK, Rotenberg, KS, Influence of a Standard Meal on the Absorption of a Controlled Release Pseudoephedrine Suspension, Biopharm Drug Disp, 9, 267 (1988).

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PATENT APPLICATIONS:

1. United States Patent Application : 20040137055, Issued July 15, 2004, Inventors: Criere, Bruno, Suplie, Pascal, Chenevier, Philippe, Qury, Pascal, Rotenberg, Keith S., and Bobotas, George. Pharmaceutical composition containing fenofibrate and method for the preparation thereof.

2. United States Provisional Patent Application: 60/618181, filed December 1, 2004, Inventors: Doyle, Ralph, Kling, Doug, Rongen, Roelof and Rotenberg, Keith. System and Method of Treating Metabolic Syndrome with Fenofibrate.

3. United States Patent Utility filed: Docket number: 026392-00030, filed February 2, 2005, Inventors: Fawzy, Abdel, Bobotas, George, Rotenberg, Keith. Composition, System and Method of Treatment of Gastrointestinal Disorders with Nizatidine Oral Solution.

4. United States Provisional Patent Application: 60/633125, Filed December 6, 2004, Inventors: Bobotas, George, Chagam, Shoba, Fawzy, Abdel, and Rotenberg, Keith. Treatment with Fenofibrate and Omega-3 Fatty Acids and a Combination Product Thereof

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